10/019087
531 Rec'd PCT/ 19 DEC 2001

Attorney's Docket No. **9250-5ctip4XX** PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE (DO/EO/US)
In re: Fischer et al.
International Appl. No. PCT/US01/18611
International Filing Date: 8 June 2001
For: METHOD FOR DETECTING A LIPOPROTEIN-ACUTE PHASE PROTEIN COMPLEX AND PREDICTING AN INCREASED RISK OF SYSTEM FAILURE OR MORTALITY

December 19, 2001

BOX PCT
Commissioner for Patents
Washington, DC 20231

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PRELIMINARY AMENDMENT

Sir:

Please amend the above-referenced application as follows. Attached hereto is a marked-up version of the changes made to the specification including the claims by the current amendment. The marked-up version of the changes is captioned "**Version With Markings To Show Changes Made**."

IN THE SPECIFICATION:

On page 1, at lines 10-17, please replace the first paragraph with the following:

This application is a National Phase application of PCT/US01/18611 filed on June 8, 2001, to be published in English, which claims priority from United States patent application 09/591,642, filed June 9, 2000, and is a continuation of United States patent application 09/591,642, filed June 9, 2000, which is a continuation-in-part of U.S. patent application 09/244,340 to Toh et al., filed February 4, 1999 and U.S. patent application 09/372,954 to Toh et al., filed August 12, 1999, the subject matter of each being incorporated herein by reference. This application also relates to U.S. patent 5,646,046 to Fischer et al., the subject matter of which is incorporated herein by reference.

IN THE CLAIMS:

Please replace Claims 14, 15, 17 and 40 with the following.

14. (Amended) The method according to claim 1, wherein the formation of the precipitate is measured at least once after time at zero.

15. (Amended) The method according to claim 14, wherein a single endpoint measurement is made of precipitate formation after time at zero.

17. (Amended) The method according to claim 10, wherein the amount of fibrin polymerization in the method causes no change in optical transmittance.

40. (Amended) A method comprising:

a) providing a test sample from a test subject;

b) adding a reagent to said test sample in order to cause formation of a complex of one or more lipoproteins and one or more acute phase proteins;

c) measuring the formation of the complex; and

d) correlating the formation of the complex to a concentration of said one or more lipoproteins.

REMARKS

Please enter this amendment prior to the calculation of the filing fee. The above amendments are made to fully recite the claims of priority for this application and to place the claims in the form in which they were pending in the parent application serial no. 09/591,642 ("the '642 application") at the time of filing of this national phase application. In addition, Claim 40 is amended above to address an objection in the Final Official Action mailed September 25, 2001 in the '642 application. The '642 application is being abandoned in favor of this application solely for the purpose of responding to the pending objections to the specification and drawings of the '642 application as recited in the Official Actions mailed September 25, 2001 and April 18, 2001 in that case. Applicants believe that no new significant matter is added by the specification and figures in this application as compared to the '642 application. In any event, as the claims are identical to those in the '642 patent, Applicant submits they are fully enabled by the disclosure of the '642 patent.

Applicants note that the claims stood rejected in the Final Official Action under 35 U.S.C. § 103(a) over United States Patent No. 5,169,786 to Carroll et al. ("Carroll") and Rowe et al. (Clin Exp. Immunol 58:237-244, 1984)("Rowe") in view of Canivet et al. (Acta Anaesthesiological Belgica 40(4): 263-268, 1989)("Canivet"). Applicants respectfully submit that such a rejection is not supported as the cited references cannot be properly combined to arrive at the present invention. The reasons for patentability relative to these references will now be briefly addressed to expedite prosecution of this matter.

To establish a prima facie case of obviousness, the prior art reference or references when combined must teach or suggest *all* the recitations of the claim, and there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. M.P.E.P. § 2143. The mere fact that references can be combined or modified does not render the resultant combination

obvious unless the prior art also suggests the desirability of the combination. M.P.E.P. § 2143.01, citing *In re Mills*, 916 F.2d 680, 16 U.S.P.Q.2d 1430 (Fed. Cir. 1990). To support combining references, evidence of a suggestion, teaching, or motivation to combine must be **clear and particular**, and this requirement for clear and particular evidence is not met by broad and conclusory statements about the teachings of references. *In re Dembiczak*, 50 U.S.P.Q.2d 1614, 1617 (Fed. Cir. 1999). The Court of Appeals for the Federal Circuit has further stated that, to support combining or modifying references, there must be **particular** evidence from the prior art as to the reason the skilled artisan, with no knowledge of the claimed invention, **would have selected these components for combination in the manner claimed**. *In re Kotzab*, 55 U.S.P.Q.2d 1313, 1317 (Fed. Cir. 2000).

Respectfully, the Final Official Action mailed September 25, 2001 failed to meet the requirements for a showing of obviousness under § 103. First, as will be discussed below, the cited combination of references fails to teach all of the recitations of the claims. Furthermore, the references cannot properly be combined in the manner relied on for the rejections.

Claim 1 recites "while causing substantially no fibrin polymerization". Thus, the instant invention, as recited in Claim 1, is concerned with monitoring the **pre-coagulation phase** of an APTT-like waveform, and is not concerned with fibrin polymerization. In contrast, Carroll examines the rate of observed clot formation (see abstract thereof). As Carroll requires observation of clot formation, while Claim 1 is carried out while causing substantially no fibrin polymerization, the procedure of Carroll would be rendered inoperative if modified to carry out the present invention. Nothing in the remaining references would cure this inoperability; nothing in the remaining references discloses or suggests monitoring such a pre-coagulation phase. Furthermore, given that Carroll would be rendered inoperative, there is clearly no **particular** evidence from the prior art as to the reason the skilled artisan, with no knowledge of the claimed invention, **would have selected these components for combination in the manner claimed**. *See, In re Kotzab*, 55 U.S.P.Q.2d at 1317.

Rowe carries out their investigations with complicated protein/lipoprotein isolation techniques such as gel filtration, ultracentrifugation and immunoelectrophoresis. The techniques described by applicants are substantially more simple and suitable for automated implementation in a clinical laboratory. Nothing in Rowe suggests how such techniques would be implemented in the form suitable for clinical screening as has been done by applicant. Canivet uses techniques such as immunoassay and electrophoresis (see page 264, column 1 thereof) but, again, these are distinct from the techniques described in Carroll and the person of ordinary skill would not be motivated to combine the two. The rejections in the Final Official Action mailed September 25, 2001 failed to provide the particular motivation for the combination relied on to support the rejections. Not only is there no such particular motivation for the advance combination, as Carroll concerns a blood coagulation assay, and as Rowe concerns protein/lipoprotein assay techniques as described above, a person of ordinary skill in the art would not be lead to combine the teachings of Rowe (or Canivet) with Carroll.

The Final Official Action mailed September 25, 2001 stated that persons of ordinary skill would modify the references "by substituting the heparin with C-reactive protein." However, as heparin is an external, exogeneous anti-coagulant administered to patients as a therapeutic, and C-reactive protein is an internal, endogenous assay target, it is respectfully submitted that one would not be motivated to replace a therapeutic agent being administered to a patient with a protein endogeneous to a patient to produce a new assay.

While the remarks set forth above are respectfully submitted to be generally responsive to the rejection of Claims 1-48, it is also respectfully submitted that none of the cited references, alone or in combination, disclose or suggest step (e) of Claim 18 or step (d) of Claim 32, or step (d) of Claim 40. Applicants note that the Final Official Action stated that Claims 1-49 were rejected as obvious. However, Applicants note that no such art rejection as to Claim 49 was advanced in the Official Action mailed April 18, 2001, as Claim 49 was only rejected under Section 112,

which rejections were overcome prior to the mailing of the Final Official Action. No grounds for rejecting Claim 49 were advanced in the Final Official Action, which merely responded to arguments presented previously by the Applicants. Accordingly, Applicants submit that no grounds for rejecting Claim 49 were pending in the '642 application.

For the foregoing reasons, it is respectfully submitted that Claims 1-49 are non-obvious over Carroll, Rowe and Canivet.

Respectfully submitted,

Robert W. Glatz
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20792
PATENT TRADEMARK OFFICE

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Michele P. McMahan
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d) correlating the formation of the complex to a concentration of said one or more lipoproteins.

END

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